OVERVIEW OF IMAZALIL RISK ASSESSMENT

Introduction

The Agency has completed its review and announces the tolerance reassessment decision for imazalil. This decision also releases to the public the human health assessment, as presented fully in the document entitled "Imazalil Tolerance Reassessment Eligibility Decision (TRED)" dated July 12, 2002, and related documents supporting this decision. The purpose of this overview is to assist the reader by identifying the key features and findings of the risk assessment in order to enhance understanding of the conclusions reached in the tolerance reassessment decision. The Agency's reassessment of aggregate risk, including exposure through food, drinking water, and residential exposure is required by the Federal Food, Drug, and Cosmetic Act (FFDCA). The Agency must review tolerances and tolerance exemptions that were in effect when the Food Quality Protection Act (FQPA) was enacted in August 1996 to ensure that these existing pesticide residue limits for food and feed commodities meet the safety standard of the new law.

FFDCA requires the Agency to review all the tolerances for registered chemicals in effect on or before the date of the enactment of FQPA. In reviewing these tolerances, the Agency must consider, among other things, aggregate risks from non-occupational sources of pesticide exposure, whether there is increased susceptibility to infants and children, and the cumulative effects of pesticides with a common mechanism of toxicity. The tolerances are considered reassessed once the safety finding has been made or a tolerance revocation occurs.

FQPA requires that the Agency, when considering whether to establish, modify, or revoke a tolerance, consider "available information" concerning the cumulative effects of the particular pesticide's residues and "other substances that have a common mechanism of toxicity." The Agency does not, at this time, have sufficient reliable information available to determine whether imazalil has a common mechanism of toxicity with other substances. Therefore, for the purposes of this risk assessment, the Agency has not assumed that imazalil has a common mechanism of toxicity with other substances. If EPA identifies other substances that share a common mechanism of toxicity with imazalil, a cumulative risk assessment for those substances will be performed.

The Agency is currently engaged in the Reregistration Eligibility Decision (RED) process for imazalil. The RED docket for imazalil was opened on March 27, 2002, and public comments on the Agency's human health and environmental risk assessments for imazalil were solicited. Completion of the non-dietary portions of the RED, however, is awaiting submission and review of data from the Registrant concerning the appropriate cancer model to employ: either the standard linear low dose cancer model ("Q_1*"), or a threshold cancer model. In its current dietary risk assessment, the Agency has used the Q_1* model, and even with this more conservative model, has determined that there is a reasonable certainty that no harm will result

from aggregate exposure to imazalil when considering dietary exposure and all other non-occupational sources of pesticide exposure for which there is reliable information. This risk estimate is likely to improve if EPA ultimately determines that a threshold cancer model is more appropriate. Therefore, EPA is proceeding to issue the tolerance reassessment for imazalil, and will complete the RED process at a later date, after the cancer model data has been analyzed and any worker and/or environmental risks have been mitigated. Imazalil has no residential uses.

Use Profile

- **Fungicide (systemic)**: Registered for post-harvest treatment of citrus fruits, for seed treatment of barley and wheat prior to planting, and in egg handling facilities. There is also an import tolerance for bananas.

- **Formulations:** Formulated as impregnated material (14.9% active ingredient(ai)), liquid (up to 31% ai), emulsifiable concentrate (up to 68.25% ai), and flowable concentrate (10% ai).

- **Methods of Application:** Applied by seed treatment equipment, drenches, smoke generators, fruit waxing equipment, and hand held equipment.

- **Use Rates:** For treating citrus, the maximum rate by wax treatment is 2,000 ppm (1.665 lb/100 gal). The seed treatment maximum application rate is 0.01008 lb ai/100 lb(slurry-type seed treatment). In egg handling facilities (hatchery and equipment), the maximum rates are 0.00032 lb/1,000 ft^3 for spray and 0.022 lb/1,000 ft^3 for smoke generator.

- **Annual Poundage:** Estimates for total annual domestic use averages approximately 6 thousand pounds of active ingredient. Crops with the highest percent crop treated are grapefruit, tangerines, lemons, and limes. In terms of pounds applied, oranges, grapefruit, and lemons account for the greatest agricultural use.

- **Pending Food Uses**: Previously submitted petitions to add certain new uses and to establish new tolerances for pears, melons, and sweet corn will be assessed during the development of the RED. Although the current dietary risk assessment does not specifically address these potential uses, the Agency intends to evaluate the impact of adding these uses on the dietary risk cup, prior to completing the RED.

- **Registrants:** Jansen Pharmaceutica (basic producer) and Makhteshim-Agan of North America

Human Health Risk Assessment

Acute Dietary Risk (Food)

(For a complete discussion, see section 4.2 of the Human Health Risk Assessment)

Acute dietary risk is calculated considering foods eaten in one day (consumption) and imazalil residue values in or on the food eaten by the general population and each population subgroup of interest. (Dietary risk from consumption of drinking water is discussed in subsequent sections). The consumption distribution can either be multiplied by a residue point estimate for a deterministic-type (i.e., Tier I/II) exposure assessment, or used with a residue distribution in a Tier III probabilistic-type (Monte Carlo) exposure assessment. A risk estimate that is less than 100% of the acute Population Adjusted Dose (aPAD) (the dose at which an individual could be exposed on any given day that would not be expected to result in adverse health effects) is not of concern to the Agency.

The Agency performed a probabilistic Tier 3 (Monte Carlo) acute dietary exposure assessment to estimate the dietary risks associated with the reregistration of imazalil. To estimate dietary exposure, the Agency used USDA Pesticide Data Program (PDP) monitoring data, field trial data, and calculated livestock anticipated residues (ARs). For all PDP analyses below the Limit of Detection (LOD), the Agency assigned a value equal to ½ LOD (weighted average of all laboratory limits of detection) where the crop was known to be treated with imazalil.

Acute risk estimates from exposures to food, associated with the use of imazalil are not of concern to the Agency. The estimated acute dietary risk (food only) is 15% of the aPAD at the 99.9th percentile for the sub-population, females (13-50 years). (The Agency identified only one suitable endpoint and sub-population for assessing acute dietary risk.)

- The Dietary Exposure Evaluation Model (DEEM™) was used to estimate acute dietary exposures from consumption of foods that contain imazalil residues.

- The most significant contributors to estimated exposure were grapefruit (~14%), oranges (~54%), and bananas (~28%), all of which were derived from USDA/PDP monitoring data.

- The toxicological endpoint selected for the acute dietary assessment is based on an increased incidence of resorptions and decreased number of fetuses from a developmental toxicity study in rabbits (NOAEL= 5 mg/kg/day) where the LOAEL is 10 mg/kg/day. This developmental endpoint is applicable only to females 13 – 50 years old.

- The Uncertainty Factor is 100X; 10X to account for interspecies extrapolation and10x to account for intraspecies variability.

- The FQPA Safety Factor is 3X for both the acute and chronic assessments due to the absence of acute, subchronic, and developmental neurotoxicity studies. The use of an additional 3X factor for the chronic assessment was warranted due to susceptibility of neonates observed in the two-generation reproduction study in rats. As a consequence, the safety factor was retained at 10X for the assessment of chronic dietary risk and reduced from 10X to 3X for the assessment of acute dietary risk for females 13 – 50 years old.

- The acute Population Adjusted Dose (aPAD) is 0.017 mg/kg/day (acute reference dose (RfD) 0.05 mg/kg/day ÷ 3X FQPA safety factor) and is only applicable to Females, 13-50 years old.

Chronic Dietary Risk (Food)

(For a complete discussion, see section 4.2 of the Human Health Risk Assessment)

Chronic dietary risk (food only) is calculated by using the average consumption value for food and average residue values on those foods over a 70-year lifetime. A risk estimate that is less than 100% of the chronic RfD (the dose at which an individual could be exposed over the course of a lifetime and no adverse health effects would be expected) is not of concern to the Agency. The cPAD is the chronic reference dose (cRfD) adjusted for the FQPA Safety Factor.

Chronic risk estimates from exposures to food are not of concern to the Agency. The chronic dietary (food only) risk estimate is <3% of the cPAD, for the U.S. Population and all subpopulations at the 99.9th percentile of exposure.

- The toxicity endpoint for the chronic dietary assessment is based on systemic toxicity, decreased body weight gain, increased liver weight, and increased liver enzyme activity oberved in a one year chronic toxicity study in the dog. These effects were observed at 20 mg/kg/day (LOAEL).(NOAEL = 2.5 mg/kg/day).

- The Uncertainty Factor is100X; 10X for inter-species variation and 10X for intra-species extrapolation.

- The FQPA Safety Factor was retained at 10X. EPA retained the factor for chronic exposure scenarios because of qualitative evidence of increased susceptibility following pre- and postnatal exposure to imazalil in a 2-generation reproduction study in rats in addition to the data gapes noted above for acute, subchronic, and developmental neurotoxicity studies.

- The major contributors to estimated imazalil chronic exposure were represented by USDA PDP monitoring data.

- The chronic Population Adjusted Dose (cPAD) is 0.0025 mg/kg/day (chronic RfD 0.025 mg/kg/day ÷ 10X FQPA safety factor).

Cancer Dietary Risk (Food)

(For a complete discussion, see section 4.2 of the Human Health Risk Assessment)

Like chronic dietary risk, cancer dietary risk (food only) is calculated by using the average consumption values for food and average residue values for those foods over a 70-year lifetime. The chronic exposure value is typically combined with a linear low-dose (Q1*) approach to determine the lifetime (cancer) risk estimate. The Agency generally considers risks greater than the 1×10^{-6} range (i.e., greater than one in one million) to exceed its level of concern for cancer dietary exposure.

As discussed above, the Agency has not yet made a final determination for imazalil concerning whether the linear low-dose (Q_1*) model or a threshold cancer model is most appropriate. The registrant is currently conducting studies to address this issue. In the interim, the Agency has utilized the more conservative standard Q_1* model in the current risk assessment. The cancer dietary risk estimate for imazalil using the Q_1* model is 2.1×10^{-6} $(mg/kg/day)^{-1}$, which is within the range of cancer risks for which Agency does not have a concern.

- Imazalil was classified as "[l]ikely to be carcinogenic in humans" in EPA's July 1999 Draft Guidelines for Carcinogenic Assessment; however, as stated above, the Agency is awaiting the results of further testing before making its final carcinogenicity finding.

- Based on current science policy and absent information confirming the mode of action in test animals, EPA quantified the human cancer risk by a linear low-dose (Q_1^*) extrapolation. The most potent unit risk for imazalil, based on male mouse liver adenoma and/or carcinoma combined tumor rates, is 6.1×10^{-2} $(mg/kg/day)^{-1}$ in human equivalents.

- The three most significant contributors to the estimated cancer risks are bananas (11%), grapefruit (20%), and oranges (38%).

Drinking Water Dietary Risk

(For a complete discussion, see section 4.3 of the Human Health Risk Assessment)

Drinking water exposure to pesticides can occur through groundwater and surface water contamination. EPA considers both acute (one day) and chronic (lifetime) drinking water risks and uses either modeling or actual monitoring data, if available, to estimate those risks. To determine the maximum allowable contribution of treated water allowed in the diet, EPA first looks at how much of the overall allowable risk is contributed by food, then calculates a "drinking water level of comparison" (DWLOC) to determine whether modeled or monitoring levels exceed this level.

The Agency uses a DWLOC as a surrogate to capture risk associated with exposure from pesticides in drinking water. The DWLOCs represent the maximum contribution to the human diet that may be attributed to residues of a pesticide in drinking water after dietary exposure is

subtracted from the aPAD or cPAD. Risks from drinking water are assessed by comparing the DWLOCs to the estimated environmental concentrations (EECs) in surface water and groundwater. Drinking water modeling is considered to be an unrefined assessment and provides high-end estimates.

In this case, the Agency concludes that no population group is exposed to imazalil residues in drinking water at a level that poses an acute, chronic, or cancer risk of concern. The EEC levels for all populations do not exceed acute, chronic, or cancer DWLOC levels.

- Estimated drinking water concentrations for ground water are based on the SCI-GROW model, which is a Tier I assessment that provides a high-end estimate.

- Estimated drinking water concentrations for surface water are based on the GENEEC model, which is a Tier I assessment that also provides a high-end estimate.

- For acute risk, potential exposure to imazalil from drinking water derived from surface water does not exceed the Agency's level of concern. Neither the surface water acute EEC of 0.072 ppb nor the groundwater estimate of "negligible" exceeds the DWLOC of 500 for females 13-50 years.

- For chronic risk, the EECs for surface water (GENEEC, 0.013 ppb) and groundwater (SCI-GROW, 0 ppb) were less than the chronic DWLOC (87 ppb for general population and 25 ppb for children 1-6 years), indicating that chronic exposure to imazalil in food and water is not of concern.

- For cancer, the estimated drinking water risk from surface water is 2.1×10^{-8}.

Residential Risk

There are no residential uses of imazalil currently registered nor any uses of imazalil in or around the home, around public buildings or recreational areas where children might be exposed.

Aggregate Risk

(For a complete discussion, see section 5.0 of the Human Health Risk Assessment)

The aggregate risk assessment for imazalil examines the combined risk from exposure through food and drinking water only because there are no residential uses for imazalil. Exposures to imazalil from dietary (food and water) sources are not of concern, as discussed above.

Tolerance Reassessment Summary

This document addresses 34 tolerances, 32 of which were in existence in August 1996 and are considered reassesssed. Tolerances for residues in/on plant commodities are established under 40 CFR §180.413(a). They are currently expressed in terms of the combined residues of imazalil [1-(2-(2,4-dichlorophenyl)-2-(2-propenyloxy)ethyl)-1*H*-imidazole] and its metabolite R014821 [1-(2,4-dichlorophenyl)-2-(1*H*-imidazole-1-yl)-1-ethanol]. The qualitative nature of the residue in plants is adequately understood. The Agency has determined that the current tolerance expression for plant commodities is appropriate.

Tolerances for residues in *animal commodities* are established under 40 CFR §180.413(b). They are currently expressed in terms of the combined residues of imazalil and its metabolites R014821 and R042243 [3-[1-(2,4-dichlorophenyl)-2-(1*H*-imidazole-1-yl)ethoxyl]-1,2-propanediol]. The tolerance expression for animal commodities listed under 40 CFR §180.413(b) should be amended to regulate imazalil and any metabolite containing the 2,4-dichlorophenyl moiety. Because of issues related to residue analytical methods, EPA hereby defines a list of marker metabolites representing the 2,4-dichlorophenyl group moiety. The total toxic residues will then be adjusted using the ratios of imazalil and the marker metabolites that were found in the animal metabolism studies. The marker compounds in milk and ruminant tissues are imazalil, FK772, and FK284; these marker compounds collectively represent the following percentages of the total toxic residues, as determined by the ruminant metabolism studies: 21% in milk, 72% in muscle, 71% in kidney, 44% in liver, and 33% in fat. The marker compounds in eggs and poultry tissues are imazalil, FK858, and FK326 or FK259; these marker compounds collectively represents the following percentages of the total toxic residues, as determined by the poultry metabolism studies: 69% in eggs, 45% in liver, 52% in fat, and 100% in muscle.

The Table below summarizes EPA's tolerance reassessment decision for imazalil, which accounts for 32 tolerance reassessments.

TOLERANCE REASSESSMENT SUMMARY FOR IMAZALIL

Commodity	Current Tolerance, ppm	Reassessed Tolerance, ppm	Comment *[Correct Commodity Definition]*
Tolerances Established Under 40 CFR §180.413(a)			
Bananas (Whole)	3.00	3.0	The tolerance for banana pulp should be revoked because it is the Agency policy to establish a tolerance on the whole commodity (including peel after removing and discarding crown tissue and stalk). The available data on banana pulp may be used for the purpose of dietary risk assessment.
Bananas (Pulp)	0.20	Revoke	
Barley, grain	0.05	0.1	A higher tolerance is needed to reflect the sensitivity of the data-collection method and to account for apparent residues in/on control grain samples.
Barley, straw	0.5	0.5	
Citrus fruit (POST-H)	10.0	10.0	
Citrus oil	25.0	200	Data from citrus processing studies showed that imazalil residues do not concentrate in juice, but do concentrate in oil.

(Table continued)

Commodity	Current Tolerance, ppm	Reassessed Tolerance, ppm	Comment *[Correct Commodity Definition]*
Citrus pulp (dried)	25.0	25	
Cottonseed	0.05	Revoke	The tolerance should be revoked because there are no registered uses of imazalil on cottonseed, and no registrants have committed to support imazalil use on cottonseed.
Wheat, forage	0.5	0.5	
Wheat, grain	0.05	0.1	A higher tolerance is needed to reflect the sensitivity of the data-collection method and to account for apparent residues in/on control grain samples.
Wheat, straw	0.5	0.5	
Tolerances To Be Proposed Under 40 CFR §180.413(a)			
Barley, hay	None established	0.5	The available data for barley forage and straw will be translated to barley hay.
Wheat, hay	None established	0.5	The available data for wheat forage and straw will be translated to wheat hay.
Tolerances Established Under 40 CFR §180.413(b)			
Cattle, fat	0.01	0.05	Tolerances for animal muscle, fat, meat by-products, liver, and milk are increased based on feeding studies.
Cattle, liver	0.50	0.2	
Cattle, meat	0.01	0.05	
Cattle, mbyp	0.01	0.05	
Goats, fat	0.01	0.05	
Goats, liver	0.50	0.2	
Goats, meat	0.01	0.05	
Goats, mbyp	0.01	0.05	
Hogs, fat	0.01	Revoke	No reasonable expectation of finite residues, therefore this tolerance is not necessary. (40 CFR 180.6(a)(3)
Hogs, liver	0.50	Revoke	No reasonable expectation of finite residues, therefore this tolerance is not necessary. (40 CFR 180.6(a)(3)
Hogs, meat	0.01	Revoke	No reasonable expectation of finite residues, therefore this tolerance is not necessary. (40 CFR 180.6(a)(3)
Hogs, mbyp	0.01	Revoke	No reasonable expectation of finite residues, therefore this tolerance is not necessary. (40 CFR 180.6(a)(3)
Horses, fat	0.01	Revoke	No reasonable expectation of finite residues, therefore this tolerance is not necessary. (40 CFR 180.6(a)(3)
Horses, liver	0.50	0.2	Tolerances for animal muscle, fat, meat by-products, liver, and milk are increased based on feeding studies.
Horses, meat	0.01	0.05	
Horses, mbyp	0.01	0.05	
Milk	0.01	0.05	
Sheep, fat	0.01	0.05	
Sheep, liver	0.50	0.2	
Sheep, meat	0.01	0.05	
Sheep, mbyp	0.01	0.05	

The Codex Alimentarius Commission has established several maximum residue limits (MRLs) for imazalil in/on various raw agricultural commodities. The Codex MRLs are expressed in terms of imazalil *per se*. The Codex MRLs and the U.S. tolerances are incompatible with respect to the tolerance expression. The U.S. tolerances for plant commodities are in expressed terms of the combined residues of imazalil and its metabolite R014821. The expression of U.S. tolerances for animal commodities will be amended to include imazalil and any metabolite containing the 2,4-dichlorophenyl moiety. Both Codex and U.S. have established MRLs/tolerances for bananas, citrus fruits, and wheat grain, forage, hay, and straw. However, the residue levels are not in harmony presumably because of differences in agricultural practices.

Summary of Pending Data

The Agency expects to receive additional studies on imazalil in July, 2002. The registrant is trying to demonstrate the mode of (cancer) action for Imazalil is either unique to laboratory animals or such that the pesticide should be regulated as a threshold carcinogen. The registrant voluntarily elected to conduct the following studies:

- Determination of Acute and Subacute Hepatocyte Cell Proliferation in Mice by BrdU Labeling

In addition, the following confirmatory data requirements have been initially identified by the Agency:

Toxicology Data for OPPTS Guidelines:

- 870.6300 Developmental Neurotoxicity in Rats
- 870.6200 Acute Neurotoxicity Study in Rats
- 870.6200 Subchronic Neurotoxicity Study in rats

Product and Residue Chemistry Data for OPPTS Guidelines:

- 860.1340 Residue analytical Method - Animal Commodities
- 860.1360 Multiresidue Method
- 860.1480 Egg and poultry fumigation Study

Occupational Exposure Data for OPPTS Guidelines

- Exposure study of citrus treatment applicators (wax application and foamers)
- Post application inhalation and dermal exposure following smoke generator or spraying applications in chicken hatcheries